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Melanoma of the nail apparatus: a systematic review and meta-analysis of current challenges and prognosis

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Abstract

Nail apparatus melanoma (NAM) is a rare dermatologic malignancy. Its prognosis is poor because it is often diagnosed late. However, progression and survival of NAM patients have only been studied among small populations. Early biopsy could help to identify suspicious lesions at a less invasive stage. While surgery is generally seen as the treatment of choice, the extent of excision margins and the use of sentinel biopsy remain debated. This systematic review aims to summarize the treatment procedures and observed prognosis in the literature during the last two decades and present pooled survival and progression rates of NAM by using meta-analysis. A systematic review on studies assessing pathology, treatment and prognosis of NAM was carried out up to end of 2018. After evaluation of eligible studies, the main emerging topics were outlined and pooled survival outcomes estimated. A total of 30 articles out of 624 identified records were included for systematic review. Finally, meta-analysis of pooled mortality rates including 18 studies was 4.6 x 100 patient-years (95% CI: 2.7, 6.8) equivalent to 5-year cumulative survival of 77.0%. Additionally, the pooled progression rate based on 17 studies was 6.3 x 100 patient-years (95% CI: 4.1, 8.9) with estimated 5-year cumulative progression-free survival of 68.5%. While the optimal extent of surgical treatment remains debated, prompt biopsy could help to identify early lesions. This is the first study to present pooled survival and progression rates by meta-analysis.

Keywords:

Melanoma; Meta-analysis; Nail apparatus; Prognosis; Survival

Introduction

Nail apparatus melanoma (NAM) is an infrequent subtype of cutaneous melanoma, that originates from the nail.¹⁻⁵ The epidemiology of NAM varies among ethnicities, with incidence rates from 0.31-1.5% in Caucasian populations,^{6,7} and with a relative frequency of up to 20% among all melanomas in Africans and Asians.^{8,9} An incidence peak is observed around the sixth life decade,^{6,10} even though single paediatric cases have also been described.¹¹⁻¹³

The aetiology of the disease remains inconclusive. Many factors such as the role of trauma, exposure to UV-light or family history have been discussed in the literature with conflicting results.^{6,14-18} NAM shows a poorer prognosis than other melanomas. The causative role of a more aggressive tumour behaviour had long been a widely accepted opinion.¹⁹⁻²² However, delay in diagnosis due to late presentation of the patients, insufficient biopsy material or misdiagnosis, especially in early disease stages, were recently discussed.^{4,9,23-27}

Due to its bad prognostic reputation, amputation of the affected (part of the) digit has been a commonly accepted approach.²⁸⁻³⁰ Lately, more conservative surgical treatments were used with no difference concerning survival outcome but superior results regarding functionality and cosmesis, thus resulting in a better quality of life.^{29,31}

However, up to date only small population studies about the outcome of NAM have been performed given the rarity of the disease. To our knowledge, this study is the first to present pooled survival and progression rates of NAM by using meta-analysis.

Methods Systematic review

Search strategy

This systematic review including meta-analysis was performed following the PRISMA guidelines. A literature search was conducted in Ovid MEDLINE and Scopus from January 2000 to December 2018. The following search terms, their synonyms or respective combinations were applied: subungual, nail apparatus, nail bed, nail matrix, melanoma, cancer and neoplasm. The search strategy was validated by the inclusion of two key articles (Ogata et al.,³² Tan et al.¹⁰) known by the authors to fit the field of the systematic review. The final search string can be found in appendix 1.

Study selection

Initial results were exported from the databases into an Excel file (Microsoft) and selection decisions documented therein. The result lists were merged and duplicates eliminated. Title, abstracts and publication type were screened for inclusion in full-text assessment. Criteria leading to study exclusion were language other than English, French or German, letters, comments, non-human or ex-vivo studies, reviews and case reports with less than two cases. No geographical restrictions were applied.

Full-text assessment of all available articles was performed by applying inclusion and exclusion criteria. Included studies reported both histopathologic (tumor thickness and/or stage) and prognostic data (follow-up and outcome) on nail apparatus melanoma (NAM). NAM was defined as melanoma of the nail bed, matrix or periungual skin. Outcome was defined as death or recurrence. Publications without differentiation between NAM and other tumors of the nail apparatus or melanoma at different sites were excluded.

Data collection

After evaluation of all selected studies, data from each publication was extracted and subclassified including year of publication, time period, number of patients, age, gender distribution, tumor site, tumor thickness, tumor stage, number of sentinel lymph node biopsies (SLNB), type of surgery, follow-up time, number of recurrence and number of death (Table 1). Finally, the essential topics from the papers were discussed in more detail and a meta-analysis of recurrence and survival rates performed.

Statistical analysis

In order to pool survival outcomes across different studies, a meta-analysis was conducted by including studies with at least 10 patients with available follow-up data and with a mean age of 50 years or more.

More specifically, the incidence rate of both overall death and NAM progression was estimated by considering the number of reported events at the numerator and the total person-time at the denominator. Person-time was calculated as the time, in years, from baseline since last visit or first recorded event and estimated from the reported mean total follow-up time and mean time to progression. When only the median follow-up time was available, it was taken as a proxy for the mean. Weighted estimates were, then, produced by using random-effects meta-analysis of rates and reported along with their 95% confidence intervals (CI). In case of zero events, a continuity

correction was applied. I^2 index was produced as well along with its p-value in order to assess overall heterogeneity across studies. All tests were considered statistically significant at $p < 0.05$. Analyses were performed with Meta-XL v.5.3 (EpiGear International Pty Ltd.).

Results

A total of 624 articles were identified. Thereof, 173 duplicates were eliminated. All remaining abstracts were screened and 33 articles were excluded due to non-human, ex vivo character of the study or a language other than English, German or French. 85 letters to the editor, reviews or comments were excluded. Full-text assessment of 322 records (11 without full-text access) resulted in 30 eligible articles by exclusion of 292 articles according to the inclusion and exclusion criteria declared above in this article (Figure 1).

Study characteristics

The 30 included, predominantly retrospective, observational single center studies from Australia, Europe, The Americas and Asia published between 2000 and 2018 represented a time period from 1914 to 2017 with a total of 1340 cases of nail apparatus melanoma. The number of patients per study varied between 2 and 157. 9 studies were restricted to NAM in situ^{31,33–39} or minimally invasive ($<0.5\text{mm}$) melanoma.²⁰

Details about gender distribution were available in 28 studies and showed a male/female ratio between 0.3-2.5:1.^{10,19,34–43,20,44–51,22,26,29–33} Information on population age was given in 28 studies with a reported average age between 41.1 and 67 years (age range: 5-94 years).^{15,19,34–40,45–47,20,48,50–52,22,26,29–33} 818 of the NAM were located on the hand and 522 lesions on the foot.

Pathology

Tumor thickness was reported in 29 studies. Mean Breslow values were available from 12 studies with unselected tumor thicknesses and ranged from 0.82 to 8.70 mm.^{22,26,50,52,30,40,41,43,45,46,48,49}

Ulceration status was mentioned with rates between 8.3% and 70.8% in 13 studies.^{10,19,45,46,49,22,26,29,32,41–44} Sentinel lymph node biopsy (SLNB) was performed in 12 studies and positivity rates varied between 0% and 30.6%.^{10,19,50,51,26,30,42–44,46,47,49} Predominant histogenetic melanoma subtypes were acral lentiginous melanoma, nodular melanoma and superficial spreading melanoma.^{10,19,41,42,46,20,22,26,29–31,33,34} Application of immunohistochemistry staining including S-100, HMB-45, Melan A or Ki67 in selected cases was reported.^{10,32,36–}

^{38,40,49,50} Investigation of molecular mutations in NAM was uncommon. Only one of the included studies assessed BRAF V600E, NRAS and cKIT mutations.¹⁹

Treatment

Wide local excision

A non-amputational surgical approach was chosen in 403 cases (30.0%). 17 studies reported performance of “en bloc” wide local excision including the distal pulp of the digit, proximal and two lateral nail folds.^{20,31,43,45,47–49,52,32–37,39,40} Two studies reported “extended en bloc” or “functional surgery” excision through additional amputation of the most distal part of the distal phalanx.^{29,38,44}

Applied lateral and proximal safety excision margins from the nail plate or clinically apparent lesion were inconsistent and ranged from 5-10mm for both in situ^{20,31,33,35,45,47,49–51} and invasive melanomas^{32,45,47–49,52} or were indistinct with 3-5mm or “wide” or “generous”.⁴³ Deep margin resection included^{31,32,39,47,49,52} or excluded^{20,29,35,36,38,40,50,51} the periosteum.

Besides healing by secondary intention^{33,34,36,39,48} different defect reconstruction techniques were chosen. In the most frequent approach, a full-thickness skin graft (FTSG) was harvested from forearm,³¹ lower abdomen,⁵⁰ groin,⁴⁷ inner arm^{20,39} or thigh.³⁹ Other sporadically used defect covering techniques were flag,^{35,52} Foucher,⁵² cross-finger³⁸ or interpolated flaps.⁵⁰

Reconstruction could be immediate^{20,31,39,49,52} or delayed.^{31,50,52}

Amputation

In 700 cases (52.5%), amputation was the treatment of choice and consisted in the partial or full resection of one or more phalanges and/ or metacarpal or metatarsal bones. Reported levels of amputation were (ranging from distal to proximal) the partial amputation of the distal phalanx, distal interphalangeal joint, median phalanx, proximal interphalangeal joint, metacarpal-/metatarsophalangeal joint, metacarpal/metatarsal and carpometacarpal joint.^{10,15,43–}

^{46,48,50,51,19,29,30,32,33,38,41,42}

Functional outcome

Conservative treatment followed by skin reconstruction or secondary intention healing resulted in the majority in high patient satisfaction with mostly good cosmetic outcome.^{31,33,36,45,47,50}

Functional impairment due to hypoesthesia or hypersensitivity, discomfort while gripping or

reduced pulp mobility mostly resolved within maximally one year postoperatively with minimal influence on quality of life.^{31,36,45,50} Lee et al.⁴⁷ demonstrated significant superior functional assessment scores in patients treated by WLE compared to amputation. Persistent pain was reported as a surgery-related symptom.^{33,36,50}

Adjuvant therapies

Only few studies included in this systematic review mentioned adjuvant approaches in metastatic NAM. The use of chemotherapeutical agents such as Dacarbazine⁴¹ or Cytosan⁵¹ was reported in two studies. Immunotherapies with Interferon alpha⁴¹ or Ipilimumab⁵¹ were described. One study mentioned the administration of irradiated autologous melanoma cells in 70 patients.¹⁵

Prophylactic isolated limb perfusion was applied in designated patients in a time period before abandoning the procedure due to absent survival improvement.⁴²

Prognosis

Mortality and progression rates were analyzed by using meta-analysis and the overall estimates were a weighted average of all study rates. Based on 18 studies included in this analysis, the final pooled mortality rate (Figure 2) was 4.6 x 100 patient-years (95% CI: 2.7, 6.8), which is equivalent to an estimated 5-year cumulative survival of 77.0%. Yet, two studies^{19,41} showed higher mortality rates.

Regarding the progression-rate (Figure 3), the overall pooled estimate, based on data of 17 studies, was 6.3 x 100 patient-years (95% CI: 4.1, 8.9), with an estimated 5-year cumulative progression-free survival of 68.5%. Only the study of Reilly et al.¹⁹ showed a higher progression rate (25.0 x 100 patient-years).

For both outcomes, the overall heterogeneity across studies was significantly high (>90%, $p < 0.001$). There was a visible trend towards lower rates over time, although this was not statistically significant.

Associated factors

Seven authors performed analysis of factors potentially influencing DFS (disease-free survival).^{19,26,29,30,32,42,43} Tumor thickness,^{26,29,30,32} tumor stage,⁴² ulceration,²⁶ mitoses,⁴² positive sentinel node²⁶ and location on the foot²⁶ showed significant association with DFS in the

respective groups. In contrast, the level of amputation was not significantly associated with decreased DFS.^{29,30,42}

Analysis of factors possibly related to survival outcome was performed in ten reports.

Tumor stage^{10,15,22,42} seemed related with overall or disease-specific survival in four study populations. Three out of five studies^{10,15,22,26,30} showed significant association between tumor thickness and survival in their respective samples upon analysis. Ulceration was negatively associated with survival outcome in three of four studies.^{10,15,19,26} In the study by Nunes et al.,²⁶ positive SLNB was found to correlate with a worse prognosis. In addition, Bormann et al.⁴¹ found a significant correlation between concomitant trauma in NAM and lower survival rates. The level of resection was not shown to influence survival outcome in any of the studies.^{30,42,48}

Discussion

Few existing literature has reported the way of treatment and oncologic prognosis of nail apparatus melanoma. In this systematic review, we aimed to outline open issues regarding surgical procedures and outcome of this rare melanoma subset.

Sentinel lymph node biopsy of melanomas provides important prognostic information and the outcome provides additional information for the management and treatment of the patient.⁵³

Positive sentinel rates appear high in tumors of the nail apparatus and are discussed to reflect the locally advanced nature of the primary lesions at first encounter with a professional or a high number of patients undergoing SLNB.^{10,19,42,43} Yet, a correlation between tumor thickness and sentinel positivity has not been demonstrated.¹⁹ Additionally, the appropriate moment for sentinel examination remains debated. Unsuitable biopsy techniques can lead to substantial discrepancy between initial tumor thickness on the obtained specimen and the postoperative Breslow thickness after final resection.^{19,43} As such divergence affects the subsequent diagnostic management of the patient (such as SLNB) complete excisional biopsy should always be applied.

However, existing data on the application of SLNB in NAM is a rarity and mostly of low evidence making definitive conclusions impossible and underscoring the need for SLNB-directed research trials in NAM. While surgery is generally seen as the most adequate therapeutic approach, clear orientation guidelines are absent for the surgical treatment of NAM and current standards for primary cutaneous melanoma are of limited use in the nail area.^{45,51,54–58} Thus, the radicality of resection differed widely between all reviewed studies. Neither varying levels of amputation^{30,32,42,48} nor WLE^{29,44,45,48} have been shown to impact survival or recurrence outcomes.

The debate about oncologic safety, and thus the most favorable level of resection, goes along with the unique anatomy of the nail apparatus,^{15,40,49} the short matrix-to-bone distance^{49,59} and the frequently irregular borders of NAM due to scattered proliferating melanocytes.^{10,20,33,34,38,39} Both present a challenge with regard to the potential risk of bone involvement and sufficient excision margins, in particular, when keeping in mind the observed difference between initial biopsy and final postoperative tumor thickness.^{10,19,43,50} Furthermore, these obstacles combined with varying size and site of the melanoma within the nail apparatus³³ might explain inconsistent surgical margins^{20,33,45,49} and variable implementation of periosteal resection^{20,31,32,36,49,52} during WLE throughout literature and may represent an ongoing ambiguity. Further, subsequent amputation has been observed in individual cases with in situ melanoma due to positive excision margins.⁴³ However, some authors have suggested WLE as a reasonable approach for in situ^{33,43} and minimally invasive lesions.^{20,45,49} While keeping oncologic safety the unconditional priority, preservation of functionality through conservative en bloc surgery should be aimed in non-invasive lesions. In our opinion, the earliest possible confirmation of a suspected NAM by biopsy seems fundamental to allow consideration of a more or less radical surgical method. Yet, we feel that investigation of a larger population might help to address this debated topic soundly. Above all, clinical examination and dermoscopy for life is crucial regardless of the chosen surgical approach.

Besides discussion about the best treatment strategy, NAM is generally accepted to have a poor prognosis. However, only small study populations have been examined. To our knowledge, our data is the first to present pooled survival and progression rates. Interestingly, progression rates seem roughly consistent despite the high heterogeneity of studies whereas survival analysis presented a more diverse result. Two studies observed higher mortality rates, which might be explained by the increased average tumor thickness (4.5mm¹⁹ and 3.5mm⁴¹) in these reports compared to others.

There may be a risk of referral bias when assessing studies on NAM as all populations included herein were seen in specialized centers. However, this rare melanoma in the nail region demands expertise and thus the vast majority of cases may be treated within such setting. Small sample sizes and selected populations limit the applicability of our findings because the reported results vary considerably across studies. Additionally, due to the scarcity of NAM patients it cannot be precluded that few patients have been included in several papers evaluated for this meta-analysis. Nevertheless, we could demonstrate an estimated trend from existent reports on survival and highlight the most important gaps of evidence in order to target future research.

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Figure Legends

Figure 1 – Flow of information during the different phases of systematic review.

Figure 2- Forest plot of mortality rates for all studies included

Mortality and progression rates were analyzed by using meta-analysis and the overall estimates were a weighted average of all study rates. Based on 18 studies included in this analysis, the final pooled mortality rate was 4.6 x 100 patient-years (95% CI: 2.7, 6.8), which is equivalent to an estimated 5-year cumulative survival of 77.0%.

Figure 3- Forest plot of mortality rates for all studies included

Regarding the progression-rate, the overall pooled estimate, based on data of 17 studies, was 6.3 x 100 patient-years (95% CI: 4.1, 8.9), with an estimated 5-year cumulative progression-free survival of 68.5%.

Appendix

Search string Ovid Medline

1. (nail* adj2 apparat* adj2 melanom*).ab,kw,ti.
2. (ungual* adj2 melanom*).ab,kw,ti.
3. (subungual* adj2 melanom*).ab,kw,ti.
4. (nail* adj2 melanom*).ab,kw,ti.
5. (("nail bed" adj2 melanom*) or ("nail matrix" adj2 melanom*)).ab,kw,ti.
6. ((nail* adj2 apparat* adj2 cancer*) or (ungual* adj2 cancer*) or (subungual* adj2 cancer*) or (nail* adj2 cancer*) or ("nail bed" adj2 cancer*) or ("nail matrix" adj2 cancer*)).ab,kw,ti.
7. ((nail* adj2 apparat* adj2 maligna*) or (ungual* adj2 maligna*) or (subungual* adj2 maligna*) or (nail* adj2 maligna*) or ("nail bed" adj2 maligna*) or ("nail matrix" adj2 maligna*)).ab,kw,ti.
8. ((nail* adj2 apparat* neoplasm*) or (ungual* adj2 neoplasm*) or (subungual* adj2 neoplasm*) or (nail* adj2 neoplasm*) or ("nail bed" adj2 neoplasm*) or ("nail matrix" adj2 neoplasm*)).ab,kw,ti.
9. exp Nail Diseases/
10. exp Melanoma/
11. exp Skin Neoplasms/
12. 9 and 10 and 11
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 12

Search string Scopus

(TITLE-ABS-KEY ("nail apparatus W/2 melanoma") OR TITLE-ABS-KEY ("ungual melanoma") OR TITLE-ABS-KEY ("subungual melanoma") OR TITLE-ABS-KEY ("nail melanoma") OR TITLE-ABS-KEY ("nail bed W/2 melanoma") OR TITLE-ABS-KEY ("nail matrix W/2 melanoma") OR TITLE-ABS-KEY ("nail apparatus W/2 cancer") OR TITLE-ABS-KEY ("ungual cancer") OR TITLE-ABS-KEY ("subungual cancer") OR TITLE-ABS-KEY ("nail cancer") OR TITLE-ABS-KEY ("nail bed W/2 cancer") OR TITLE-ABS-KEY ("nail matrix W/2 cancer") OR TITLE-ABS-KEY („nail OR apparatus W/2 maligna ") OR TITLE-ABS-KEY(„ungual maligna") OR TITLE-ABS-KEY ("subungual maligna") OR TITLE-ABS-KEY ("nail bed W/2 maligna") OR TITLE-ABS-KEY ("nail matrix W/2 maligna") OR TITLE-ABS-KEY ("nail apparatus W/2 neoplasm") OR TITLE-ABS-KEY ("subungual neoplasm") OR TITLE-ABS-KEY ("ungual neoplasm") OR TITLE-ABS-KEY ("nail bed W/2 neoplasm") OR TITLE-ABS-KEY ("nail matrix W/2 neoplasm"))

Table 1 – Selected studies.

Study	NAM patients (n=1340)	Average tumor thickness (mm) range	Ulceration	SLNB/ positive	WLE (n=403)	Amputation (distal/proximal) (n=700)	No treatment/ treatment unknown (n=237)	Deaths (n=346)	First disease progression (n=356)	Mean FU time (months)	Mean time to progression (months)	Restrictions
Chakera A et al., 2019	103	3.1† 0.2-13.0	54	36/10	4	98 (77/21)	1/0	31	44	105	70	NAM on hands
Nunes et al., 2018	157	8.7 NM	94	61/16	NM	NM	0/157	26	33	35.1	35.1	
Goettmann et al., 2018	63	in situ	NM	NM	56	7 (7/0)	0	0	2	120	28	in situ
Montagner S et al., 2018	21	4.0 0.31-12.0	NM	NM	12	9 (NM)	0	1	5	73	31.2	
Flores-Terry M et al., 2018	7	2.7 0.38-4.0	1	NM	5	2 (2/0)	0	1	1	46	46	
Lee KT et al., 2017	41	0.67‡ 0-3	2	17/2	41	0	0	0	2	31	22.5	WLE
Ogata D et al., 2017	151	NM	86	NM	36	113 (51/57)	0/2	27	29	113	113	
Reilly DJ	54	4.5†	34	36/11	1	49 (29/20)	0/4	22	29	31	21.2	

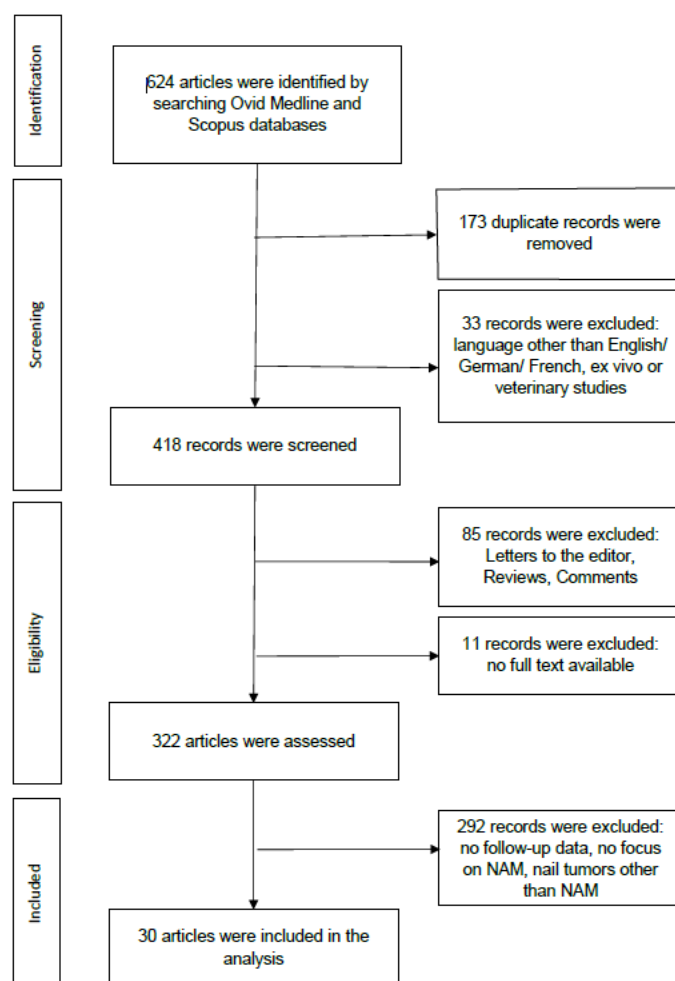
et al., 2017		0.3-18										
Anda-Juarez												
MC et al., 2016	15	in situ	NM	NM	15	0	0	0	0	55.93		in situ
Dika E et al., 2016	39	2.6† 0.4-6	24	15/3	30	9 (9/0)	0	7	10	60	67	
Duarte AF et al., 2015	6	in situ	NM	NM	6	0	0	0	0	25.2		WLE, in situ
Study	NAM patients (n=1340)	Average tumor thickness (mm) Range	Ulceratio n	SLNB/ positive	WLE (n=403)	Amputation (distal/proximal) (n=700)	No treatment/ treatment unknown (n=237)	Deaths (n=346)	First disease progression (n=356)	Mean FU time (months)	Mean time to progression (months)	Restrictions
Nakamura Y et al., 2015	50	NM 0-0.5	0	NM	50	0	0	0	5	60.8	64.4	WLE, 2 subgroups <0.5mm vs. unrestricted
Sinno S et al., 2015	18	NM <0.5-7.0	NM	10/2	7	11 (5/6)	0	3	1	34	15	NAM on hands
Lee WJ et al., 2015	49	2.54 0.23-11.0	10	NM	NM	NM	0/49	17	14	51	51	

Oh BH et al., 2015	10	0.82 0.1-4.0	NM	2/0	10	0	0	0	0	37.8		WLE
Neczyporenko F et al., 2014	11	in situ	NM	NM	11	0	0	0	2	65.5	108	WLE, in situ
Nguyen JT et al., 2013	124	3.1 0.2-20.0	NM	20/5	8	116 (18/98)	0	85	61	112.8	36	WLE excluded from survival analysis
Guarneri C et al., 2013	2	4.75 4.5-5.0	1	2/0	0	2 (1/1)	0	0	0	8.5		amputation
Sureda N et al., 2011	7	0.175 0.15-0.2	NM	NM	7	0	0	0	0	45		WLE, <0.5mm
Andre J et al., 2010	3	in situ	NM	NM	3	0	0	0	0	48		WLE, in situ
Imakado S et al., 2008	2	in situ	NM	NM	2	0	0	0	0	27		WLE, in situ
Cohen T et al., 2008	49	2.1 0.2-11	20	30/5	8	40 (2/38)	1/0	11	11	38	20.5	

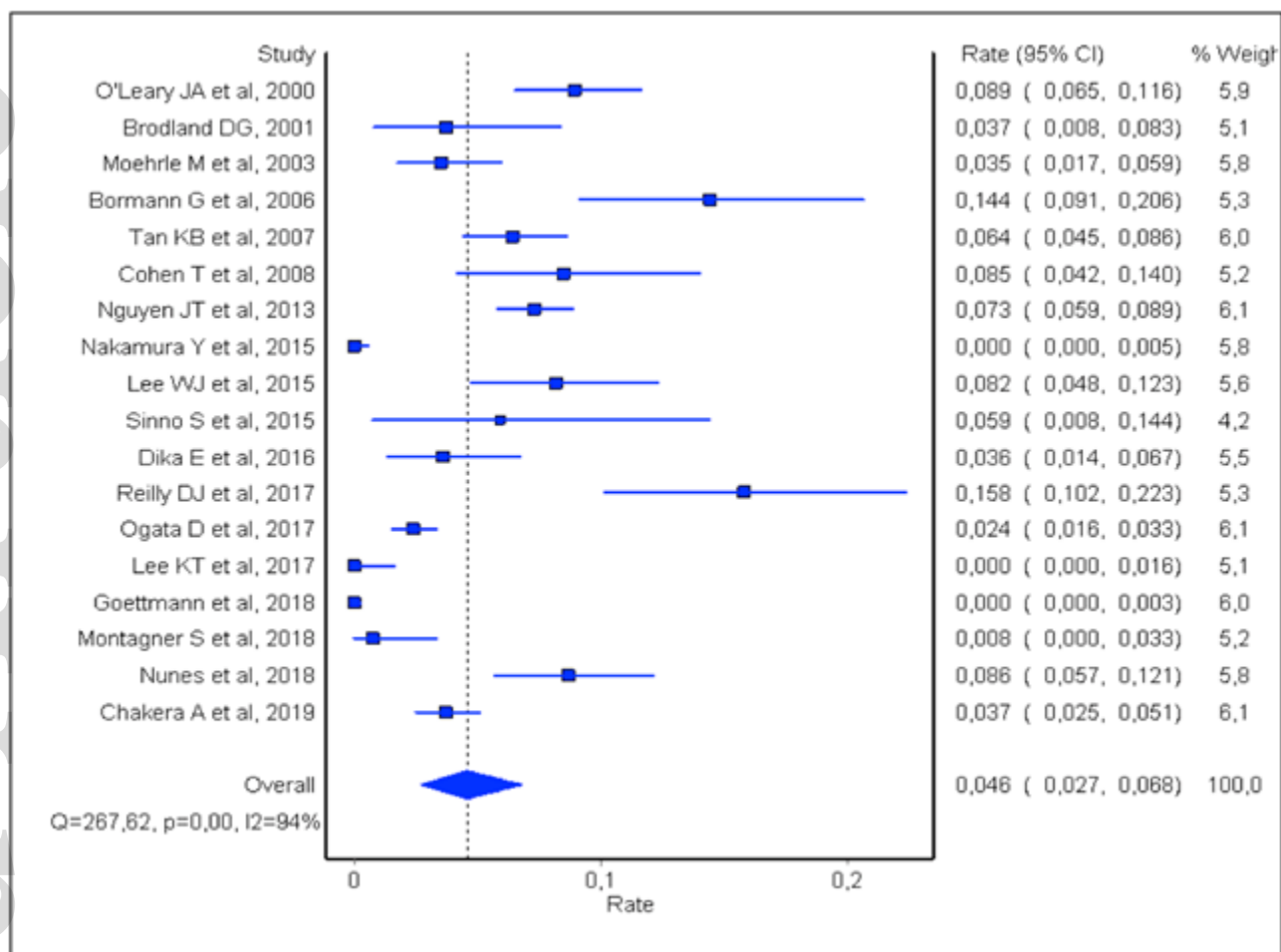
Study	NAM patients (n=1340)	Average tumor thickness (mm) range	Ulceration n	SLNB/positive	WLE (n=403)	Amputation (distal/proximal) (n=700)	No treatment/treatment unknown (n=237)	Deaths (n=346)	First disease progression (n=356)	Mean FU time (months)	Mean time to progression (months)	Restrictions
Tan KB et al., 2007	124	3.2† 0.25-14.0	35	29/7	17	85 (NM)	4/18	35	48	57.1	57.1	
Rayatt SS et al., 2007	4	2.35 0.9-4.0	NM	NM	4	0	0	1	1	94	36	WLE, NAM on thumbs
Bormann G et al., 2006	33	3.5 0.4-12.0	19	NM	0	32 (16/16)	1/0	21	17	53	53	
Lazar et al., 2005	9	in situ	NM	NM	9	0	0	0	0	50.4		WLE, in situ NAM on hands
High WA et al., 2004	7	in situ	NM	NM	4	3	0	0	1	24	5	in situ
Moehrle M et al., 2003	31 31	1.68† NM 2.65† NM	7 5	NM	31	31	0	11	36	60	60	two subgroups (WLE vs. amputation)

Brodland DG. et al., 2001	14	1.38 NM-3.3	NM	NM	14	0	0	4	4	92	67.1	WLE
O'Leary JA et al., 2000	93	NM	NM	NM	0	93	0	43		62.4		

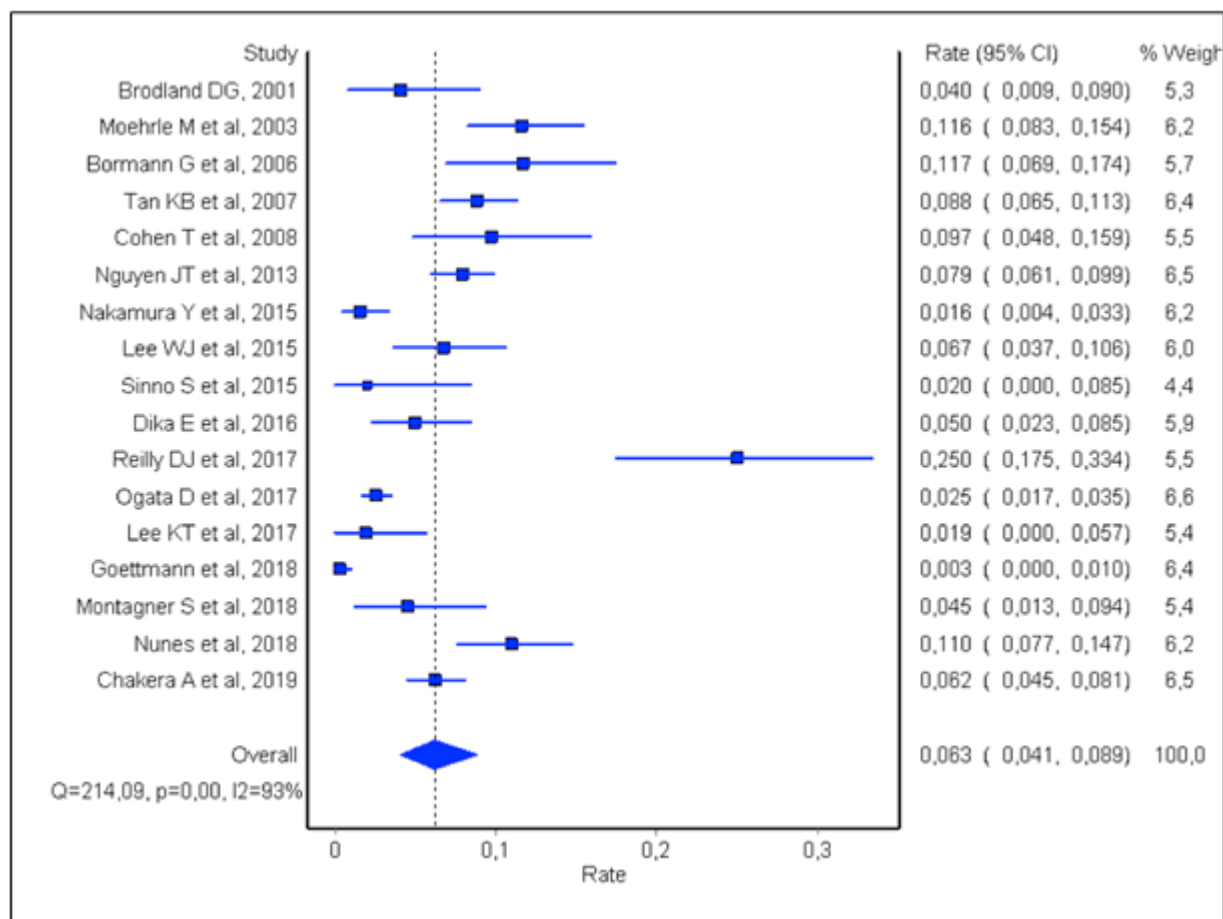
NM: Not mentioned, *AJCC 2001, **AJCC2017, †median, ‡ in situ included



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